

**REMARKS**

*Office Action*

Applicants acknowledge with thanks the Examiner's allowance of claims 1-3.

The Examiner states that the application is in condition for allowance except for the two Figures numbered Figure 8 (sheets 67 and 68). According to the Examiner, the description of the Figures on page 10 of the specification also refers to Figures 7A and 7B, but the drawing corresponding to Figure 7 does not have any subparts. The Examiner also argues that applicants have not responded to the Notice of Draftsperson's Patent Drawing Review (PTO-948), attached to the Office Action dated 12/18/00 and referencing the drawings filed 4/30/99. Applicants traverse.

The December 18, 2000 Office Action objected to the Figures, as filed on April 30, 1999. See, Exhibit A (copy of the December 18, 2000 Office Action with Notice of Draftsperson's Patent Drawing Review attached, noting objection to drawings dated 4/30/99).

At the time the December 18, 2000 Office Action was mailed, applicants had already amended the Figures to correct the mis-numbering of Figures 7 and 8. See, September 14, 1999 Preliminary Amendment ("Amendment"; see Exhibit B). On page 5 of the Amendment, applicants amended the Figure labels to correct the above-mentioned typographical error. In particular, applicants re-labeled former Figure 7 to 7A, and re-labeled the former first Figure 8 to 7B. Applicants also

Application No.: 09/303,216  
Office Action dated December 6, 2007  
Response to Office Action dated February 6, 2008

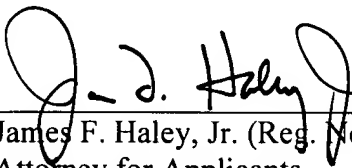
submitted copies of the original Figure 7 and the first Figure 8 with those changes entered as indicated in red. See, Exhibit C (attached to the Amendment, the marked up Figures and substitute Figures).

Applicants request that the Examiner either enter that Amendment, or if the Amendment has already been entered, withdraw the objection and allow the application.

Conclusion

Applicants request that the Examiner pass the pending claims to issue. If the Examiner believes that a telephonic interview would be helpful, she is invited to call the undersigned at any time.

Respectfully submitted,



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Attorney for Applicants  
c/o ROPES & GRAY LLP  
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# EXHIBIT A



UNITED STATES DEPARTMENT OF COMMERCE  
Patent and Trademark Office

Address: COMMISSIONER OF PATENTS AND TRADEMARKS  
Washington, D.C. 20231

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.
09/303,216	04/30/99	KIM	J VPI97-101-CI

JAMES F HALEY JR ESQ  
FISH & NEAVE  
1251 AVENUE OF THE AMERICAS  
NEW YORK NY 10020-1104

HM22/1218

EXAMINER

ALLEN, M

ART UNIT

PAPER NUMBER

1631

DATE MAILED:

12/18/00

Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

RECEIVED

DEC 21 2000

FISH & NEAVE - PATENT DEPT  
REFERRED TO LS  
BY                     

DOCKETED FOR

3/18/01

**Office Action Summary**

Application No.

09/303,216

Applicant(s)

KIM ET AL.

Examiner

Marianne Allen

Art Unit

1631

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136 (a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

- 1) ☒ Responsive to communication(s) filed on 25 September 2000.
- 2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

- 4) ☒ Claim(s) 1-24 is/are pending in the application.
- 4a) Of the above claim(s) 7-24 is/are withdrawn from consideration.
- 5) ☐ Claim(s) \_\_\_\_\_ is/are allowed.
- 6) ☒ Claim(s) 1-6 is/are rejected.
- 7) ☐ Claim(s) \_\_\_\_\_ is/are objected to.
- 8) ☐ Claims \_\_\_\_\_ are subject to restriction and/or election requirement.

**Application Papers**

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☒ The drawing(s) filed on 30 April 1999 is/are objected to by the Examiner.
- 11) ☐ The proposed drawing correction filed on \_\_\_\_\_ is: a) ☐ approved b) ☐ disapproved.
- 12) ☐ The oath or declaration is objected to by the Examiner.

**Priority under 35 U.S.C. § 119**

- 13) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).
- a) ☐ All b) ☐ Some \* c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. \_\_\_\_\_.
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).
- \* See the attached detailed Office action for a list of the certified copies not received.
- 14) ☒ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. & 119(e).

**Attachment(s)**

- 15) ☐ Notice of References Cited (PTO-892)
- 16) ☒ Notice of Draftsperson's Patent Drawing Review (PTO-948)
- 17) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) 91/2.
- 18) ☐ Interview Summary (PTO-413) Paper No(s). \_\_\_\_\_
- 19) ☐ Notice of Informal Patent Application (PTO-152)
- 20) ☐ Other:

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Applicant's election of Group I, claims 1-6, in Paper No. 8 is acknowledged. Because applicant did not distinctly and specifically point out the supposed errors in the restriction requirement, the election has been treated as an election without traverse (MPEP § 818.03(a)).

Claims 7-24 are withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected invention, there being no allowable generic or linking claim. Election was made **without** traverse in Paper No. 8.

Claims 1-6 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for the particular HCV NS3 helicase/dU<sub>8</sub> complex crystallized in the examples and the particular crystallization methods set forth therein, does not reasonably provide enablement for all crystalline compositions and methods therefore encompassed by the claims. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

The specification is directed to producing crystals of sufficient quality so as to be suitable for structural studies by X-ray crystallography.

The prior art to at least Brown et al. (Methods in Molecular Biology, 1996) makes clear that crystallization of protein-DNA complexes is not predictable and requires guidance and extensive experimentation that would not be considered routine to develop crystals suitable for X-ray crystallography. There is no general rationale in determining the best conditions for

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cocrystallizing these complexes. (See at least page 299, first full paragraph; page 300, first full paragraph; page 306, section 3.4.2; page 311, section 4 of Brown et al.) Successful purification and crystallization conditions for a particular protein/nucleic acid complex would not be expected to be predictive of the conditions required for crystallizing another complex even if it was similar. Note that the crystallization conditions for Yao et al. (Nature Structural Biology, 1997) for the helicase absent an oligonucleotide are substantially different from those of the examples.

The specification defines "HCV NS3 helicase protein" on pages 12-14 of the specification broadly and as including unrelated sequences on the N- and C-terminal ends. Also included are mutated forms with deletions, substitutions, and insertions. First of all, the specification does not clearly define the metes and bounds of those proteins included by the phrase "HCV NS3 helicase protein." Secondly, the present specification fails to provide sufficient guidance to enable one to produce the crystallizable compositions and crystallized complex encompassed by the claims such that they would be suitable for crystallization in view of the acknowledged unpredictability of producing such crystals. The specification fails to provide sufficient guidance as to those crystallization conditions or method steps that would produce crystalline compositions commensurate with the claims. As such, the specification can only be viewed as enabling the crystalline compositions specifically exemplified and those particularly exemplified methods of crystallizing them.

Applicant is advised that for purposes of enablement "crystallizable composition" and "crystallized complex" are being interpreted as suitable for producing X-ray crystallographic

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quality crystals in keeping with the specification disclosure. Furthermore, limitations such as “crystallizable composition” require actually having produced a crystal from the composition as it is not so predictable that all proteins or complexes can actually be crystallized.

Claims 1-2 and 5-6 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 2 and 6 refer to an amino acid range of SEQ ID NO: 1. However, SEQ ID NO: 1 is a DNA sequence.

Claims 1 and 6 refer to crystallizable compositions; however, these claims are confusing in that these limitations appear to be circular. That is, in step (a) of the method of claim 6, how can one obtain a crystallizable composition without already having determined that it can be crystallized? Furthermore, in step (b), subjecting the composition to conditions which promote crystallization generically may or may not result in a crystallized complex.

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless --

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.



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Claim 1 is rejected under 35 U.S.C. 102(b) as being anticipated by Morgenstern et al. (Journal of Virology, 1997).

Morgenstern et al. discloses a composition which contains an HCV NS3 helicase and an oligonucleotide. (See page 3769, left column, helicase assay.) The composition is considered to meet the limitation of crystallizable in that it could be frozen which would produce crystals. Note that the claims do not require isolated components, X-ray crystallographic quality crystals, or that the composition is actually crystallized. Further note that comprising language permits inclusion of larger sequences. The RNA substrate used is larger than 12 nucleotides in length.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Marianne P. Allen, whose telephone number is (703) 308-0666. The examiner can normally be reached on Monday-Friday from 9:00 am to 3:00 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Michael Woodward, Ph.D., can be reached on (703) 308-4028. Official FAX communications may be directed to either (703) 308-4242 or (703) 305-3014.

Any inquiry concerning the formalities of this application should be directed to Patent Analyst Tina Plunkett whose telephone number is (703) 308-0009.

Any inquiry of a general nature or relating to the status of this application should be directed to the Group receptionist whose telephone number is (703) 308-0196.

*Marianne P. Allen*  
MARIANNE P. ALLEN  
PRIMARY EXAMINER  
GROUP 1800  
44631

FORM PTO-1449

U.S. DEPARTMENT OF COMMERCE  
PATENT AND TRADEMARK OFFICEATTY. DOCKET NO.  
VPI/97-101 CIP CONSERIAL NO.  
~~Not Yet~~ *09/303416*  
AssignedINFORMATION DISCLOSURE  
STATEMENT BY APPLICANTAPPLICANT  
Kim et al.FILING DATE  
Concurrently HerewithGROUP  
~~Not Yet~~ *AU1631*  
Assigned

## U.S. PATENT DOCUMENTS

EXAMINER INITIAL	DOCUMENT NUMBER	DATE	NAME	CLASS	SUBCLASS	FILING DATE IF APPROPRIATE
	4,833,233	05/23/89	Carter	530	363	
	5,353,236	10/04/94	Subbiah	364	499	

## FOREIGN PATENT DOCUMENTS

EXAMINER INITIAL	DOCUMENT NUMBER	DATE	COUN TRY	CLASS	SUBCLA SS	TRANSLATION	
						YES	NO
	WO 92/14211	20/08/92	PCT	<del>G06F</del>	15/00		
	WO 94/25860	10/11/94	PCT	<del>G01N</del>	24/00		
<i>MPA</i>	WO 97/12043	03/04/97	PCT	<del>C12N</del> <del>C12P</del>	15/62 21/02		
	WO 97/15588	05/01/97	PCT	<del>G07K</del>	1/14		

## OTHER DOCUMENTS (Including Author, Title, Date, Pertinent Pages, Etc.)

EXAMINER INITIAL	
<i>MPA</i>	D.G. Brown et al., "Crystallography in the Study of Protein-DNA Interactions", <u>Methods in Molecular Biology</u> , 56, pp. 293-318 (1996).
	P.N. Bryan, "Protein Engineering", <u>Biotech Adv.</u> , 5, pp. 221-234 (1987).
	I.D. Campbell et al., "Diffraction, in Biological Spectroscopy", <u>The Benjamin/Cummings Publishing Company, Inc.</u> , Menlo Park, CA, pp. 299-326 (1984).
	J. Jancarik et al., "Sparse Matrix Sampling: A Screening Method for Crystallization of Proteins", <u>J. Appl. Cryst.</u> , 24, pp. 409-411 (1991).
✓	A. Kajihara et al., "Protein Modelling Using a Chimera Reference Protein Derived From Exons", <u>Protein Eng'g</u> , 6, pp. 615-620 (1993).

EXAMINER

*MPA*DATE CONSIDERED *10/10/00*

EXAMINER: Initial if citation considered, whether or not citation is in conformance with MPEP 609; Draw line through citation if not conformance and not considered. Include copy of this form with next communication to applicant.

ORM PTO-1449	U.S. DEPARTMENT OF COMMERCE PATENT AND TRADEMARK OFFICE	ATTY. DOCKET NO. VPI/97-101 CIP CON	SERIAL NO. <del>Not Yet</del> <i>09/30/21</i> Assigned
INFORMATION DISCLOSURE STATEMENT BY APPLICANT		APPLICANT Kim et al.	
		FILING DATE Concurrently Herewith	GROUP <del>Not Yet</del> <i>44/63/</i> Assigned

## OTHER DOCUMENTS (Including Author, Title, Date, Pertinent Pages, Etc.)

EXAMINER INITIAL	
<i>MPA</i>	K.A. Morgenstern et al., " Polynucleotide Modulation of the Protease, Nucleoside Triphosphatase, and Helicase Activities of a Hepatitis C Virus NS3-NS4A Complex Isolated from Transfected COS Cells", <u>J. of Virology</u> , 71, pp. 3767-3775 (1997).
↓	A.J. Russell et al., "Rational Modification of Enzyme Catalysis by Engineering Surface Charge", <u>Nature</u> , 328, pp. 496-500 (1987).
↓	U. Uhlin et al., "Crystallization and Crystallographic Investigations of Ribonucleotide Reductase Protein R1 From <i>Escherichia Coli</i> ", <u>FEBS</u> , 336(1), pp. 148-152 (1993).
↓	N.Yao et al., "Structure of the Hepatitis C Virus RNA Helicase Domain", <u>Nature Structural Biology</u> , 4, pp. 463-7 (1997).

EXAMINER *MP Allen*DATE CONSIDERED *12/12/00*

EXAMINER: Initial if citation considered, whether or not citation is in conformance with MPEP 609; Draw line through citation if not conformance and not considered. Include copy of this form with next communication to applicant.

NOTICE OF DRAFTSPERSON'S  
PATENT DRAWING REVIEWThe drawing(s) filed (insert date) 4-30-99 are:A. ☐ approved by the Draftsperson under 37 CFR 1.84 or 1.152.B. ☒ objected to by the Draftsperson under 37 CFR 1.84 or 1.152 for the reasons indicated below. The Examiner will require submission of new, corrected drawings when necessary. Corrected drawing must be submitted according to the instructions on the back of this notice.

<p>1. DRAWINGS. 37 CFR 1.84(a): Acceptable categories of drawings: Black-ink. Color. Color drawings are not acceptable until petition is granted. Fig(s) _____ Pencil and non black ink not permitted. Fig(s) _____</p> <p>2. PHOTOGRAPHS. 37 CFR 1.84 (b) 1 full-tone set is required. Fig(s) _____ Photographs not properly mounted (must use bristol board or photographic double-weight paper). Fig(s) _____ Poor quality (half-tone). Fig(s) _____</p> <p>3. TYPE OF PAPER. 37 CFR 1.84(c) Paper not flexible, strong, white, and durable. Fig(s) _____ Erasures, alterations, overwritings, interlineations, folds, copy machine marks not accepted. Fig(s) _____ Mylar, velum paper is not acceptable (too thin). Fig(s) _____</p> <p>4. SIZE OF PAPER. 37 CFR 1.84(f): Acceptable sizes: 21.0 cm by 29.7 cm (DIN size A4) 21.6 cm by 27.9 cm (8 1/2 x 11 inches) All drawing sheets not the same size. Sheet(s) _____ Drawings sheets not an acceptable size. Fig(s) _____</p> <p>5. MARGINS. 37 CFR 1.84(g): Acceptable margins: Top 2.5 cm Left 2.5 cm Right 1.5 cm Bottom 1.0 cm SIZE: A4 Size Top 2.5 cm Left 2.5 cm Right 1.5 cm Bottom 1.0 cm SIZE: 8 1/2 x 11 Margins not acceptable. Fig(s) _____ Top (T) _____ Left (L) _____ Right (R) _____ Bottom (B) _____</p> <p>6. VIEWS. 37 CFR 1.84(h) REMINDER: Specification may require revision to correspond to drawing changes. Partial views. 37 CFR 1.84(h)(2) Brackets needed to show figure as one entity. Fig(s) _____ Views not labeled separately or properly. Fig(s) _____ Enlarged view not labeled separately or properly. Fig(s) _____</p> <p>7. SECTIONAL VIEWS. 37 CFR 1.84 (h)(3) Hatching not indicated for sectional portions of an object. Fig(s) _____ Sectional designation should be noted with Arabic or Roman numbers. Fig(s) _____</p>	<p>8. ARRANGEMENT OF VIEWS. 37 CFR 1.84(i) Words do not appear on a horizontal, left-to-right fashion when page is either upright or turned so that the top becomes the right side, except for graphs. Fig(s) _____</p> <p>9. SCALE. 37 CFR 1.84(k) Scale not large enough to show mechanism without crowding when drawing is reduced in size to two-thirds in reproduction. Fig(s) _____</p> <p>10. CHARACTER OF LINES, NUMBERS, &amp; LETTERS. 37 CFR 1.84(f) Lines, numbers &amp; letters not uniformly thick and well defined, clean, durable, and black (poor line quality). Fig(s) _____</p> <p>11. SHADING. 37 CFR 1.84(m) Solid black areas pale. Fig(s) _____ Solid black shading not permitted. Fig(s) _____ Shade lines, pale, rough and blurred. Fig(s) _____</p> <p>12. NUMBERS, LETTERS, &amp; REFERENCE CHARACTERS. 37 CFR 1.84(p) Numbers and reference characters not plain and legible. Fig(s) _____ Figure legends are poor. Fig(s) _____ Numbers and reference characters not oriented in the same direction as the view. 37 CFR 1.84(p)(1) Fig(s) _____ English alphabet not used. 37 CFR 1.84(p)(2) Fig(s) _____ Numbers, letters and reference characters must be at least .32 cm (1/8 inch) in height. 37 CFR 1.84(p)(3) Fig(s) _____</p> <p>13. LEAD LINES. 37 CFR 1.84(q) Lead lines cross each other. Fig(s) _____ Lead lines missing. Fig(s) _____</p> <p>14. NUMBERING OF SHEETS OF DRAWINGS. 37 CFR 1.84(i) Sheets not numbered consecutively, and in Arabic numerals beginning with number 1. Sheet(s) _____</p> <p>15. NUMBERING OF VIEWS. 37 CFR 1.84(u) Views not numbered consecutively, and in Arabic numerals, beginning with number 1. Fig(s) _____</p> <p>16. CORRECTIONS. 37 CFR 1.84(w) Corrections not made from prior PTO-948 dated _____</p> <p>17. DESIGN DRAWINGS. 37 CFR 1.152 Surface shading shown not appropriate. Fig(s) _____ Solid black shading not used for color contrast. Fig(s) _____</p>
COMMENTS	

REVIEWER JLDATE 1-28-00TELEPHONE NO. 202 305 2430

ATTACHMENT TO PAPER NO. \_\_\_\_\_

# EXHIBIT B

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Examiner : Not Yet Assigned  
Group Art Unit : Not Yet Assigned  
Applicants : Joseph L. Kim et al.  
Serial No. : 09/303,216  
Filed : April 30, 1999  
For : CRYSTALS OF HEPATITIS C VIRUS HELICASE OR  
FRAGMENTS THEREOF COMPRISING A HELICASE  
BINDING POCKET

New York, New York  
September 14, 1999

Hon. Assistant Commissioner  
for Patents  
Washington, D.C. 20231

PRELIMINARY AMENDMENT

Sir:

Preliminary to examination of the above-identified application, kindly amend the application as follows:

IN THE SPECIFICATION

On page 1, delete the title "Hepatitis C Virus Helicase Crystals and Molecules Comprising Helicase Binding Pockets", and substitute therefor --Crystals of Hepatitis C Virus Helicase Or Fragments Thereof Comprising A Helicase Binding Pocket--.

On page 1, immediately after the title, insert

## --- CROSS-REFERENCE TO RELATED APPLICATIONS

This application is a continuing application of co-pending International Patent Application PCT/US98/16879, filed August 13, 1998, which is a continuation-in-part of United States provisional patent application 60/055,772, filed August 13, 1997. ---

Page 10, line 5, delete "is colored blue, domain 2 red, and domain 3 green. The sulfate and DNA are colored in yellow.", and substitute therefor - is located at the top left portion of the molecule containing a seventh  $\beta$ -strand running antiparallel to the rest of the sheet, domain 2 is located at the top right portion, domain 3 which is predominantly  $\alpha$ -helical is situated at the bottom portion of the molecule. The DNA that is bound in the center of the molecule and the sulfate which is bound to domain 1 are also shown.--

Page 10, line 8, delete "(blue)" and "(red)".

Page 10, line 17, delete "orange color depicts" and substitute therefor -- bright and thick lines depict --; line 19, delete "blue color depicts" and substitute therefor -- faint and thin lines depict --.

Page 54, line 12, delete " $\Delta$ ", and substitute therefor --  $\text{\AA}$  --.

## IN THE CLAIMS

In claim 11 step a., page 100, after "NS3" insert -- helicase --.

In claim 15, page 103, delete " $\Delta$ ", and substitute therefor --  $\text{\AA}$  --.

In claim 18, page 105, delete " $\Delta$ ", and substitute therefor --  $\text{\AA}$  --.

In claim 21 step a., page 107, delete "U8" and substitute therefor -- U4 --.

In claim 22, page 108, delete " $\Delta$ ", and substitute therefor --  $\text{\AA}$  --; in step a. delete "U8" and substitute therefor -- NTP --.

In claim 24, page 109, after "electron density map of" insert -- at least a portion of --.

14. (Amended) A method for evaluating the potential of a chemical entity to associate with:

a) a molecule or molecular complex comprising a binding pocket defined by structure coordinates of NS3 helicase amino acids Val232, Thr254, Gly255, Thr269, Gly271, Lys272, Ala275, Trp501 and Tyr502 according to Figure 1, or

b) a homologue of said molecule or molecular complex, wherein said homologue comprises a binding pocket that has a root mean square deviation from the backbone atoms of said amino acids of not more than 1.5 [ $\Delta$ ] Å comprising the steps of:

i) employing computational means to perform a fitting operation between the chemical entity and a binding pocket of the molecule or molecular complex; [and]

ii) analyzing the results of said fitting operation to quantify the association between the chemical entity and the binding pocket[.]; and

iii) outputting said quantified association to a suitable output hardware.

16. (Amended) A method for evaluating the potential of a chemical entity to associate with:

a) a molecule or molecular complex comprising a binding pocket defined by structure coordinates of NS3 helicase amino acids His369, Ser370, Lys371, Tyr392, Arg393, Thr411, Asp412, Ala413, Cys431, Val432, Gln434, Ile446, Thr448, Arg461, Glu493, Glu555, Asn556 and Phe557 according to Figure 1, or



b) a homologue of said molecule or molecular complex, wherein said homologue comprises a binding pocket that has a root mean square deviation from the backbone atoms of said amino acids of not more than 1.5 Å comprising the steps of:

I) employing computational means to perform a fitting operation between the chemical entity and a binding pocket of the molecule or molecular complex; [and]

ii) analyzing the results of said fitting operation to quantify the association between the chemical entity and the binding pocket[.]; and

iii) outputting said quantified association to a suitable output hardware.

17. (Amended) A method for evaluating the potential of a chemical entity to associate with:

a) a molecule or molecular complex comprising a binding pocket defined by structure coordinates of NS3 helicase amino acids Pro205, Thr206, Gly207, Ser208, Gly209, Lys210, Ser211, Thr212, Lys213, Asn229, Ala234, Gly237, Phe238, Tyr241, Asp290, Glu291, His293, Thr322, Ala323, Thr324, Gln460, Gly463, Arg464 and Arg467 according to Figure 1, or

b) a homologue of said molecule or molecular complex, wherein said homologue comprises a binding pocket that has a root mean square deviation from the backbone atoms of said amino acids of not more than 1.5 Å comprising the steps of:

I) employing computational means to perform a fitting operation between the chemical entity and a binding pocket of the molecule or molecular complex; [and]

ii) analyzing the results of said fitting operation to quantify the association between the chemical entity and the binding pocket[.]; and

iii) outputting said quantified association to a suitable output hardware.

### REMARKS

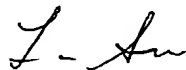
Applicants hereby amend the original title to conform with the new title established by the International Searching Authority in the International Patent Application PCT/US98/16879. Applicants have also amended the specification to refer to prior applications, revised the Description of Drawings to account for the use of black and white drawings instead of color drawings, and have amended the specification and claims to correct inadvertent typographical errors. Support for the amendments in claims 14, 16 and 17 may be found in the specification at page 31, line 12-20.

In the figures, the labels were amended to correct inadvertent typographical errors, specifically; former Figure 7 has been relabeled to 7A, and the first Figure 8 has been relabeled to 7B so that each sheet is referred to distinctly. Applicants have submitted herewith copies of the original Figure 7 and the first Figure 8 with these changes entered there as indicated in red.

These amendments add no new matter.

Applicants request consideration of the application and early allowance of the pending claims.

Respectfully submitted,



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James F. Haley, Jr. (Reg. No. 27,794)  
Attorney for Applicants  
Lisa A. Dixon (Reg. No. 40,995)  
Li Su (Reg. No. P-45,141)

Agents for Applicants  
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I Hereby Certify that ~~this~~  
Correspondence is being  
Deposited with the U.S.  
Postal Service as First  
Class Mail in an Envelope  
Addressed to: ASSISTANT  
COMMISSIONER FOR  
PATENTS  
WASHINGTON, D.C. 20231 on

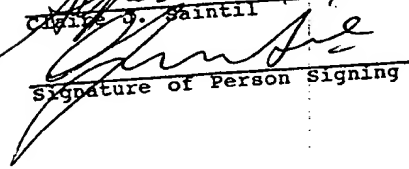
September 14, 1999  
Charles G. Saintil  
  
Signature of Person Signing

FIGURE 7A

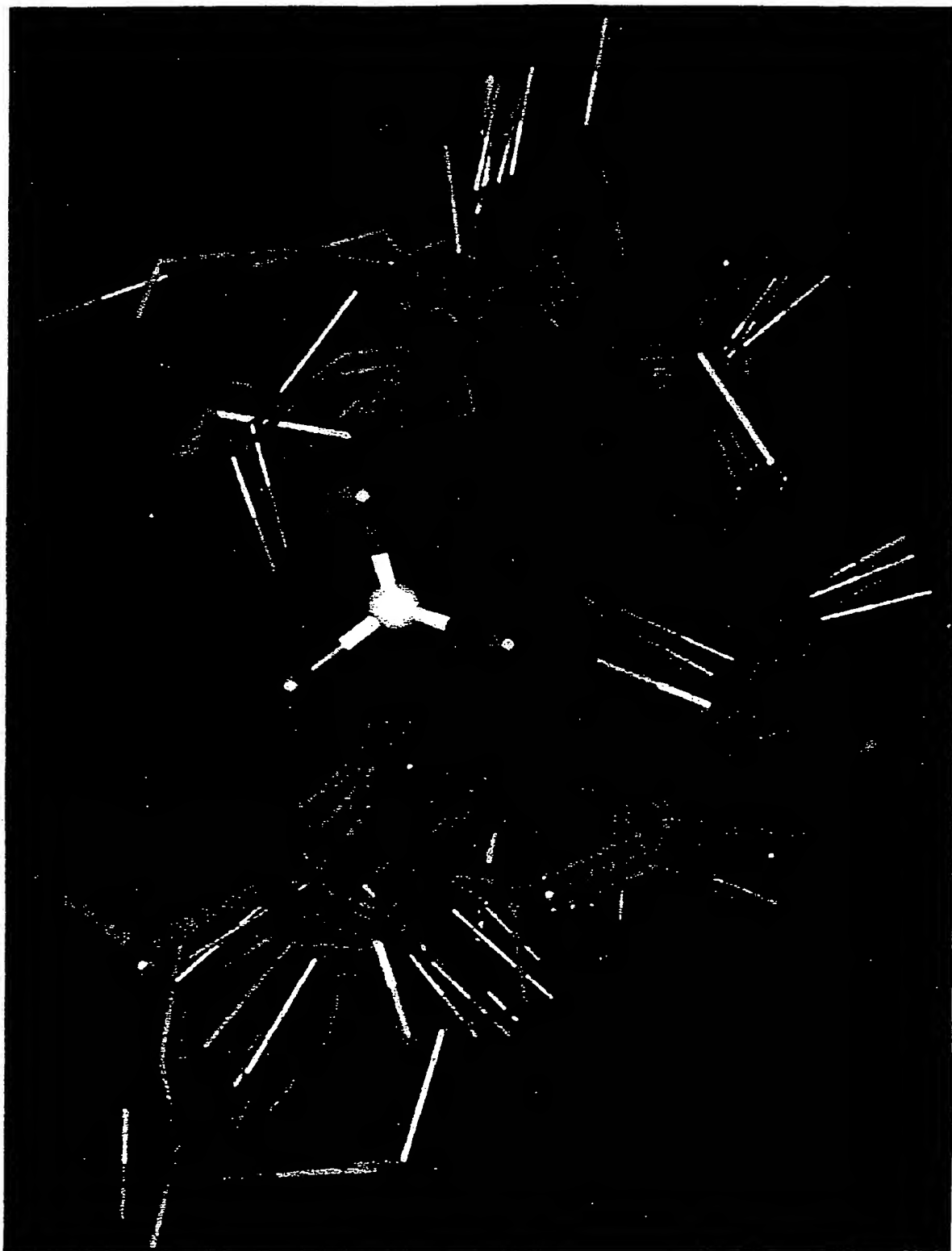


FIGURE 87B

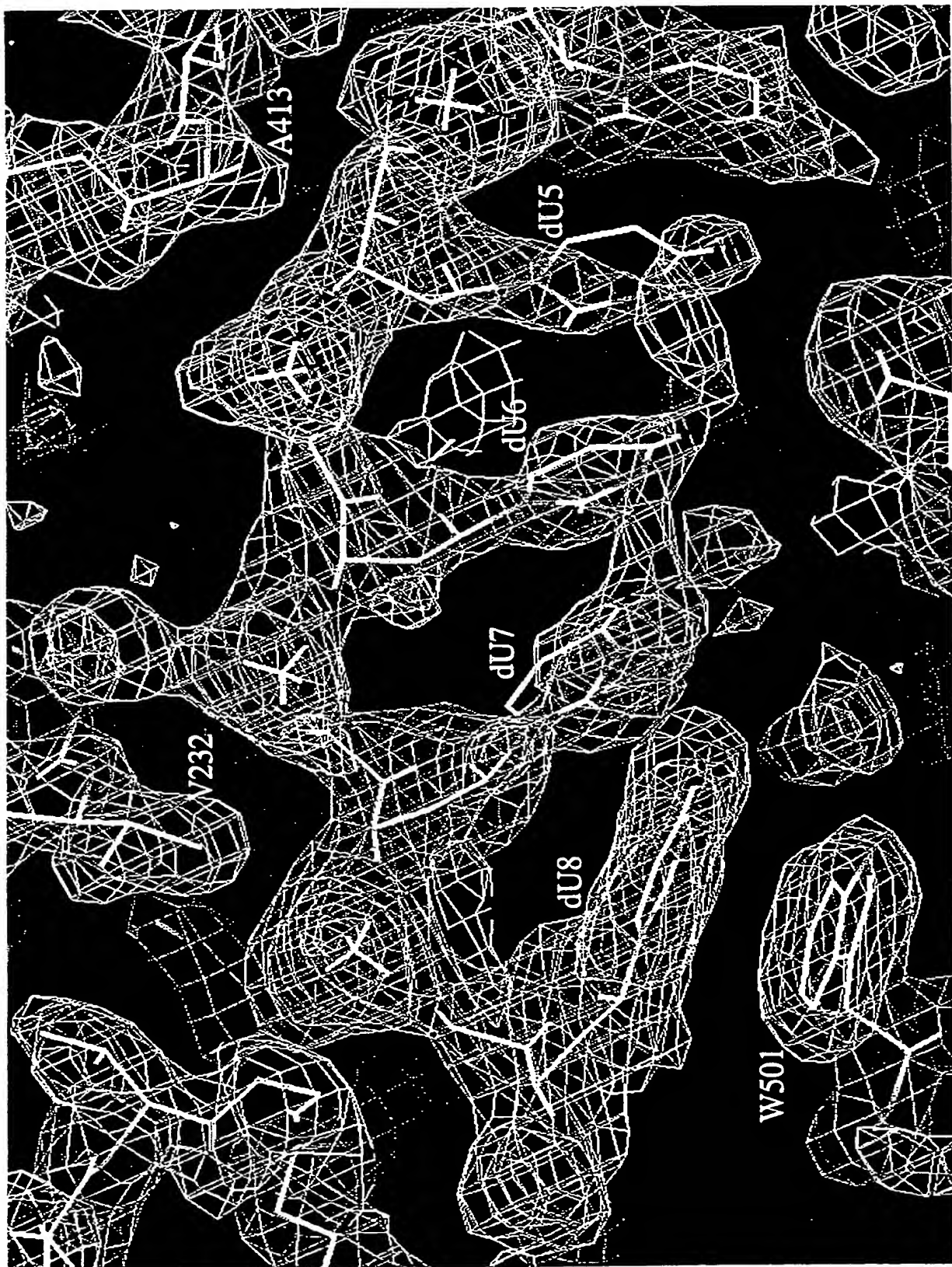


FIGURE 7A

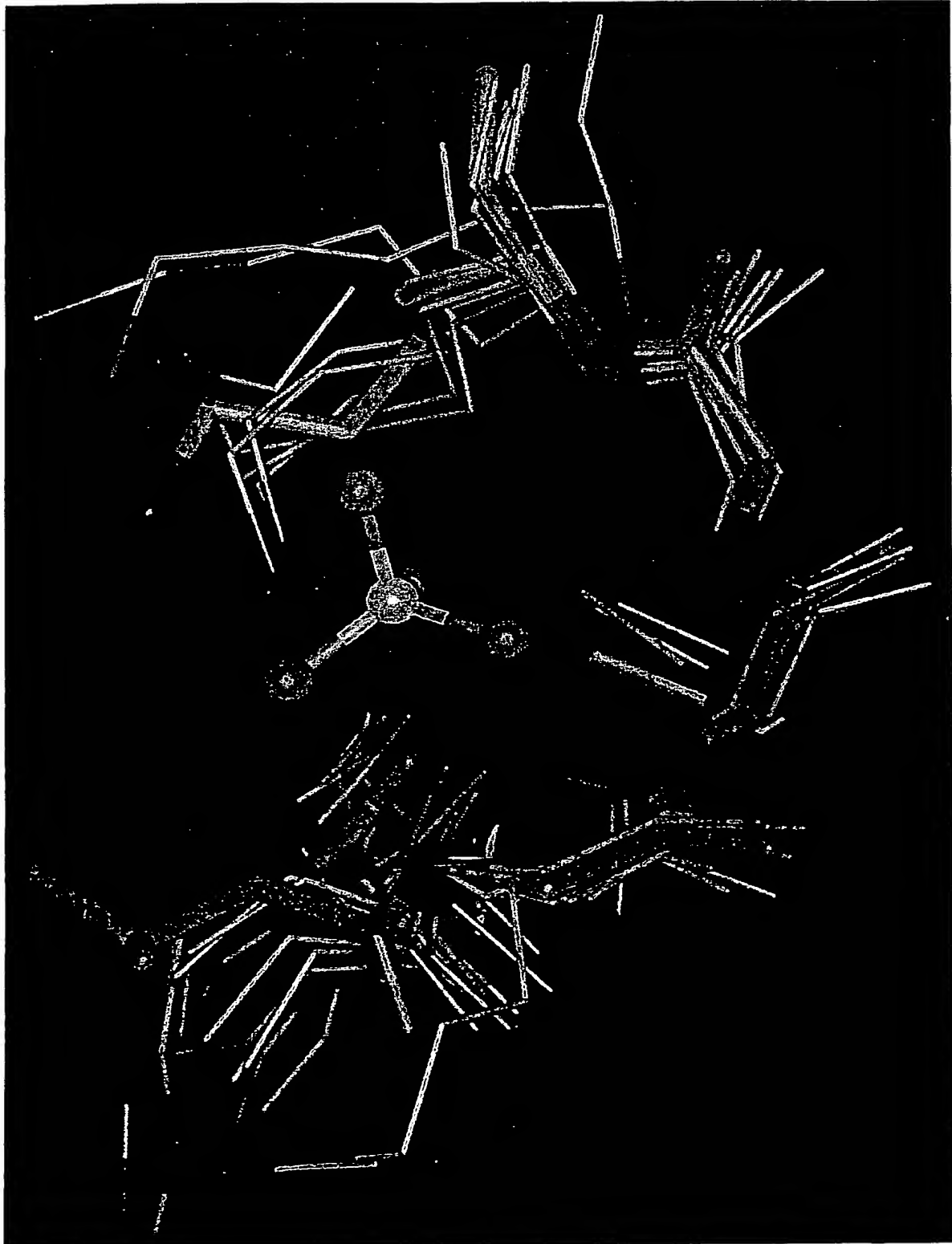


FIGURE 7B

